Effect of CYP3A5 Genotype on the Pharmacokinetics of Maraviroc and Metabolites in Healthy Subjects

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Introduction

- Maraviroc (MVC) is a substrate for cytochrome P450 3A (CYP3A), P-glycoprotein (P-gp), and organic anion transporting polypeptide 1B1 (OATP1B1)
- Previous data by Lu et al. demonstrated that MVC average exposures (C_{avg}) are 41% lower in subjects with the CYP3A5*1/*1 wild-type/extensive metabolizer (EM) genotype (n=8) compared to those with CYP3A5 mutant alleles (*3, *6, and/or *7; poor metabolizer [PM]; n=8) following a single MVC 300 mg dose[1]
- While rare in Caucasians (CAU), the prevalence of CYP3A5 EMs is substantial (39%-70%) in Blacks (including sub-Saharan Africans and African Americans [AA])[2]

Methods

- Study A4001110 was an open-label, parallel-group, multiple-dose study targeting 12 healthy adults per cohort to:
  - Assess the effect of CYP3A5 genotype on the PK of MVC and CYP3A5-derived metabolites when MVC was dosed alone or with darunavir/cobicistat (DRV/c), a potent CYP3A inhibitor combination
  - Compare MVC and metabolite PK between race in PM
- Subjects were enrolled by CYP3A5 genotype and self-reported race into 1 of 4 cohorts
  - **Cohort 1:** AA with no CYP3A5*1 alleles (PM)
  - **Cohort 2:** AA with 1 CYP3A5*1 allele (intermediate metabolizer; IM)
  - **Cohort 3:** AA with 2 CYP3A5*1 alleles (EM)
  - **Cohort 4:** CAU with no CYP3A5*1 alleles (PM)
- Subjects who had a CYP3A4*22 allele and/or had a solute carrier organic anion transporter 1B1 (SLCO1B1)*5 or *15 allele were excluded from the study as these genotypes may affect MVC metabolism thus having the potential to confound study results
- Treatment
  - **Part 1:** all subjects received MVC 300 mg BID for 5 days (fasted)
  - **Part 2** ***(Cohorts 1 and 3 only)*****:** subjects received MVC 150 mg QD in combination with DRV/c 800/150 mg QD for 10 days (with food)
    - MVC 150 mg QD (rather than recommended 150 mg BID with potent CYP3A inhibitors) was studied to assess the impact of EMs on the lower daily dose being investigated by external groups
  - No washout period required between Part 1 and Part 2
- Intensive PK sampling followed the last dose of MVC in Part 1 and Part 2
- MVC and metabolite PK parameters were calculated using non-compartmental analysis of concentration time data
- Plasma samples were analyzed for MVC and CYP3A5-derived metabolites by Covance (New Jersey, USA) and York Bioanalytical Solutions (Kent, United Kingdom), respectively
- The pharmacogenomics sample was analyzed by Pfizer Clinical Pharmacogenomics Laboratory (Connecticut, USA)
  - DNA from whole blood samples was extracted and single nucleotide polymorphisms characterized using custom TaqMan assays

Table 1. Demographic Characteristics

	Cohort 1 (n=11)	Cohort 2 (n=12)	Cohort 3 (n=12)	Cohort 4 (n=12)
Gender (n)				
Male/Female	9/2	12/0	11/1	11/1
Age (years)				
Mean (SD)	37.3 (9.7)	38.3 (10.4)	34.6 (11.4)	48.2 (6.0)
Range	29-55	21-48	20-54	40-55
Weight (kg)				
Mean (SD)	80.4 (8.9)	79.6 (11.9)	82.6 (13.3)	75.3 (10.6)
Range	59.7-90.4	61.7-96.4	60.9-110.7	62.2-96.0

SD, standard deviation.

Results

- In screening, the majority of CAU subjects were CYP3A5 PM while the majority of AA subjects were either CYP3A5 IM or EM based on the 179 subjects (**Table 2**)
- 47 subjects were assigned to the study treatment (**Table 1**)
  - Although 12 subjects/cohort were targeted, only 11 subjects were enrolled in Cohort 1 in an effort to minimize study enrollment delays (pre-specified minimum sample size=11 subjects/cohort)
- Part 1 PK – MVC 300 mg BID (**Table 3** and **Table 4/Figure 1**)
  - Geometric mean MVC AUC_t, C_{avg}, and C_{max} exposure were ranked highest to lowest by CYP3A5 genotype: PM > IM > EM
  - MVC plasma exposure based on adjusted geometric mean AUC_t, C_{avg}, and C_{max} for AA EM subjects (Cohort 3) was approximately 26%-39% lower in comparison to IM and PM subjects in Cohorts 1, 2, and 4
  - Comparing the impact of race in PM, AA (Cohort 1) had a 17% higher AUC_t and C_{avg}, and an 18% higher C_{max} compared to CAU (Cohort 4)
  - PF-06857639 was the only MVC metabolite shown to be affected by CYP3A5 genotype with AA EM (Cohort 3) demonstrating an approximate 2-fold higher $MRAUC_t$ compared to AA poor metabolizers (Cohort 1)
- Part 2 PK – MVC 150 mg QD + DRV/c 800/150 mg QD (**Table 3/Figure 1**)
  - AA EM subjects had a 17%-18% lower geometric mean MVC AUC_t and C_{avg} and a 32% lower C_{max} compared to AA PM
  - MVC metabolite exposures were low and undetectable in a substantial amount of plasma samples indicating that co-administration with DRV/c inhibited CYP3A-mediated metabolite formation (PK data not presented)
- There were no serious or severe adverse events

Figure 1. MVC C_{avg} Exposure From Part 1 and Part 2

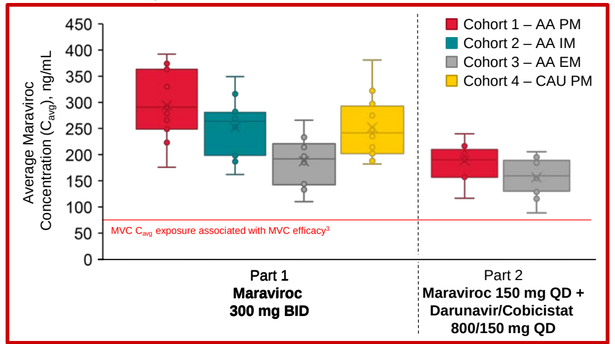

Table 2. Genotyping Results for Screening Population

	CYP3A5 Genotype			CYP3A4 Genotype			SLCO1B1 Genotype			
	2 CYP3A5*1	1 CYP3A5*1	No CYP3A5*1	2 CYP3A4*22	1 CYP3A4*22	No CYP3A4*22	2 SLCO1B1*1	1 SLCO1B1*1	Possible 1 SLCO1B1*1	No SLCO1B1*1
African American (n=135)	35 (25.9%)	69 (51.1%)	31 (23.0%)	0	0	135 (100%)	0	6 (4.4%)	4 (2.9%)	125 (92.6%)
Caucasian (n=41)	0 (0%)	2 (4.9%)	39 (95.1%)	0	4 (9.8%)	37 (90.2%)	0	2 (4.9%)	11 (26.8%)	28 (68.3%)
Other (n=3)	0 (0%)	2 (66.7%)	1 (33.3%)	0	0	3 (100%)	0	0	0	3 (100%)

Table 3. Statistical Summary of Cohort Comparison for MVC Plasma PK Parameters – Part 1 and Part 2

Parameter (unit)	Adjusted Geometric Means: Test	Adjusted Geometric Means: Reference	Ratio (Test/Reference) of Adjusted Geometric Means (90% CI)	*P* value
Part 1 – MVC 300 mg BID				
Cohort 1 - AA PM (Test) vs Cohort 4 - CAU PM (Reference)				
AUC_{12} (ng•hr/mL)	3441	2947	1.17 (0.99, 1.38)	0.1318
C_{avg} (ng/mL)	286.8	245.8	1.17 (0.98, 1.38)	0.1338
C_{max} (ng/mL)	863.9	731.0	1.18 (0.95, 1.47)	0.1997
C_{12} (ng/mL)	59.84	63.10	0.95 (0.77, 1.17)	0.6761
Cohort 2 - AA IM (Test) vs Cohort 1 - AA PM (Reference)				
AUC_{12} (ng•hr/mL)	2954	3441	0.86 (0.72, 1.02)	0.1369
C_{avg} (ng/mL)	246.2	286.8	0.86 (0.72, 1.02)	0.1370
C_{max} (ng/mL)	754.0	863.9	0.87 (0.70, 1.08)	0.2947
C_{12} (ng/mL)	63.09	59.84	1.05 (0.85, 1.30)	0.6771
Cohort 3 - AA EM (Test) vs Cohort 1 - AA PM (Reference)				
AUC_{12} (ng•hr/mL)	2181	3441	0.63 (0.54, 0.75)	<0.0001
C_{avg} (ng/mL)	181.6	286.8	0.63 (0.53, 0.75)	<0.0001
C_{max} (ng/mL)	529.0	863.9	0.61 (0.49, 0.76)	0.0004
C_{12} (ng/mL)	45.32	59.84	0.76 (0.61, 0.94)	0.0331
Cohort 3 - AA EM (Test) vs Cohort 2 - AA IM (Reference)				
AUC_{12} (ng•hr/mL)	2181	2954	0.74 (0.63, 0.87)	0.0036
C_{avg} (ng/mL)	181.6	246.2	0.74 (0.63, 0.87)	0.0036
C_{max} (ng/mL)	529.0	754.0	0.70 (0.57, 0.87)	0.0071
C_{12} (ng/mL)	45.32	63.09	0.72 (0.58, 0.88)	0.0104
Cohort 3 - AA EM (Test) vs Cohort 4 - CAU PM (Reference)				
AUC_{12} (ng•hr/mL)	2181	2947	0.74 (0.63, 0.87)	0.0038
C_{avg} (ng/mL)	181.6	245.8	0.74 (0.63, 0.87)	0.0037
C_{max} (ng/mL)	529.0	731.0	0.72 (0.59, 0.89)	0.0135
C_{12} (ng/mL)	45.32	63.10	0.72 (0.58, 0.88)	0.0104
Part 2 – MVC 150 mg QD + DRV/c 800/150 mg QD				
Cohort 3 - AA EM (Test) vs Cohort 1 - AA PM (Reference)				
AUC_{24} (ng•hr/mL)	3645	4413	0.83 (0.70, 0.97)	0.0531
C_{avg} (ng/mL)	151.7	184.1	0.82 (0.70, 0.97)	0.0507
C_{max} (ng/mL)	432.9	633.6	0.68 (0.50, 0.94)	0.0505
C_{24} (ng/mL)	56.34	56.56	1.00 (0.83, 1.19)	0.9713

BID, twice daily; CI, confidence interval; MVC, maraviroc; PK, pharmacokinetic(s).

Discussion

- Individual C_{avg} values ranged between 110-392 ng/mL and 88.1-238 ng/mL across all CYP3A5 genotype/race cohorts dosed in Part 1 and Part 2, respectively, demonstrating that all subjects enrolled into the study achieved the C_{avg} concentration shown to be associated with near maximal virologic efficacy with MVC (75 ng/mL) in the Phase 3 MERIT study[3] (**Figure 1**)
- In a post hoc analysis of the MERIT study (A4001026), where MVC was dosed at 300 mg BID in the absence of a potent CYP3A inhibitor with or without food, CYP3A5 genotype was not shown to impact MVC efficacy or MVC C_{avg} (based on population PK methods); MVC C_{avg} was not lower among CYP3A5 EM[4]

Table 4. Statistical Summary of Cohort Comparison for $MRAUC_{12}$ – Part 1

Metabolite	Adjusted Geometric Means: Test	Adjusted Geometric Means: Reference	Ratio (Test/Reference) of Adjusted Geometric Means (90% CI)	*P* value
Cohort 1 - AA PM (Test) vs Cohort 4 - CAU PM (Reference)				
PF-06857639	0.02172	0.01585	1.37 (1.12, 1.67)	0.0106
PF-06857640	0.02577	0.02338	1.10 (0.94, 1.29)	0.3081
PF-06883683	0.02048	0.02099	0.98 (0.81, 1.17)	0.8241
PF-06883686	0.02766	0.02774	1.00 (0.80, 1.24)	0.9816
Cohort 2 - AA IM (Test) vs Cohort 1 - AA PM (Reference)				
PF-06857639	0.03564	0.02172	1.64 (1.35, 2.00)	0.0001
PF-06857640	0.02621	0.02577	1.02 (0.87, 1.19)	0.8583
PF-06883683	0.02427	0.02048	1.19 (0.99, 1.42)	0.1261
PF-06883686	0.02908	0.02766	1.05 (0.85, 1.30)	0.6974
Cohort 3 - AA EM (Test) vs Cohort 1 - AA PM (Reference)				
PF-06857639	0.04312	0.02172	1.98 (1.63, 2.42)	<0.0001
PF-06857640	0.02797	0.02577	1.09 (0.93, 1.27)	0.3913
PF-06883683	0.02040	0.02048	1.00 (0.83, 1.20)	0.9708
PF-06883686	0.02795	0.02766	1.01 (0.82, 1.25)	0.9363
Cohort 3 - AA EM (Test) vs Cohort 2 - AA IM (Reference)				
PF-06857639	0.04312	0.03564	1.21 (1.00, 1.47)	0.1061
PF-06857640	0.02797	0.02621	1.07 (0.91, 1.25)	0.4866
PF-06883683	0.02040	0.02427	0.84 (0.70, 1.01)	0.1099
PF-06883686	0.02795	0.02908	0.96 (0.78, 1.19)	0.7520
Cohort 3 - AA EM (Test) vs Cohort 4 - CAU PM (Reference)				
PF-06857639	0.04312	0.01585	2.72 (2.24, 3.30)	<0.0001
PF-06857640	0.02797	0.02338	1.20 (1.02, 1.40)	0.0590
PF-06883683	0.02040	0.02099	0.97 (0.81, 1.16)	0.7913
PF-06883686	0.02795	0.02774	1.01 (0.82, 1.24)	0.9536

$MRAUC_{12}$ represents the metabolite ratios calculated as (AUC_t metabolite/AUC_t parent) × (MWparent/MWmetabolite).
BID, twice daily; CI, confidence interval; MVC, maraviroc; MW, molecular weight; PK, pharmacokinetic(s). PF-06883683 and PF-06883686 previously presented as PF-06927573 and PF-06927572, respectively.

Conclusions

- CYP3A5 genotype, not race, had the most influence on MVC exposure; however, prevalence of CYP3A5 EMs is greater in AA than CAU
- CYP3A5 genotype and associated impact on PK are not expected to be clinically relevant for the treatment of HIV as:
  - MVC exposure associated with MVC efficacy (C_{avg} ≥75 ng/mL) was achieved in all subjects receiving MVC 300 mg BID alone or MVC 150 mg QD in combination with DRV/c
  - CYP3A5 genotype was not shown to impact efficacy in the Phase 3 MERIT study
- The magnitude of the CYP3A5 genotype effect on MVC exposure was reduced in the presence of DRV/c, a potent CYP3A inhibitor combination
- Following MVC 300 mg BID, CYP3A5 genotype only impacted the exposure for one metabolite (PF-06857639); AA EMs had approximately 2-fold higher exposures compared to AA PMs which was consistent with the impact on MVC exposure for the same comparison and is not considered clinically relevant
- MVC dosed alone or co-administered with DRV/c was generally safe and well tolerated in the healthy volunteers evaluated in this study

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